Advances in
VIRUS RESEARCH

Edited by

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KARL MARAMOROSCH KENNETH M. SMITH

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KENNETH M. SMITH (1892–1981)

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KENNETH M. SMITH, CBE, FRS

The Times, London, June 12, 1981, recorded in a detailed obituary the death on June 11 of Kenneth M. Smith, CBE, FRS, at the age of 88. Dr. Smith played a dominant role in the founding of *Advances in Virus Research* and served as an editor for nearly three decades until his death.

Prior to the middle of 1952, while in the United States as a Fellow at the National Institutes of Health, Dr. Smith and Mr. Kurt Jacoby, then vice-president and treasurer of Academic Press, engaged in extensive discussion concerning the establishment of a review journal in the field of virology. Dr. Smith and Mr. Jacoby then invited a biophysicist, Max A. Lauffer, to become with Dr. Smith a member of the original editorial team. The two editors planned Volume 1, which appeared in 1953 and set the tone for the publication.

Kenneth Manley Smith was born of English parentage in 1892 near Glasgow. He was educated at Dulwich College. He served in World War I until wounded and discharged and then became lecturer in Agricultural Entomology at Manchester University. He obtained the D.Sc. degree there in 1926. In 1927 Dr. Smith was appointed entomologist to the Potato Virus Research Station of the School of Agriculture at Cambridge University and was made a member of Downing College. He was awarded the Ph.D. degree by Cambridge in 1929. When the founding director, Dr. R. N. Salaman, of the Potato Virus Research Station retired, Dr. Smith succeeded him as director. The station later became the Virus Research Unit of the Agricultural Research Council, originally associated with the Molteno Institute of Cambridge University. When he was succeeded upon retirement as director by Dr. Roy Markham, Dr. Smith remained on the research staff for two years. Then in 1963, at the age of 70, he went to the University of Pittsburgh as Visiting Professor of Biophysics for two years; after that he served until 1969 as Visiting Professor of Botany at the University of Texas, Austin. Upon returning to his home in Cambridge in 1969, he continued to be active in science as an author and editor until his death.

Many honors came to Dr. Smith. He was a Fellow of the Royal Society, Leuwenhoek Lecturer of the Royal Society, and Master's Lecturer of the Royal Horticultural Society. He was an honorary member of the Association of Applied Biologists and an honorary life member of the Society for General Microbiology. In 1956 he was made a Commander of the Order of the British Empire. From 1945 to 1950 he was a Governor of Dulwich College, and in 1953 he was made an Honorary Fellow

of Downing College. Throughout his career he had extensive experience in the United States. In 1939 he was a Fellow at the Rockefeller Institute for Medical Research at Princeton in the laboratory of Dr. Louis O. Kunkel and in 1952 he was a Fellow at the National Institutes of Health in the laboratory of Dr. Ralph W. G. Wyckoff. As already mentioned, he spent seven years following retirement at the University of Pittsburgh and at the University of Texas.

Kenneth Smith's scientific contributions were enormous. He was a pioneer in the study of insect transmission of plant viruses and in the resolution of the etiology of complex infections. Kenneth Smith was the first to recognize several new plant viruses, among them tomato bushy stunt virus, turnip yellow mosaic virus, and tobacco necrosis virus. He contributed greatly to the study of the physical properties of viruses—ultrafiltration, electron microscopy, and, in collaboration with D.E. Lea, the action of ionizing radiations on viruses.

After World War II, Dr. Smith became interested in viral diseases of insects. He was primarily responsible for discovering the cytoplasmic polyhedrosis viruses. With Professor Robley Williams of the University of California at Berkeley he did important work on the morphology of the tipula iridescent virus. After his retirement, when in Pittsburgh, he became involved in ongoing work on the entropy-driven polymerization of viral proteins, specifically that of cucumber virus 4. At Pittsburgh, and later at Texas, he also carried out research on viruses of blue-green algae. His experimental work was published in a vast number of scientific articles. In addition, he was the author of many reviews published in prestigious journals, the author of chapters in reference works, and the author of "A Textbook of Plant Virus Diseases," published in 1937 and revised in 1957 and 1972, "Insect Virology," first published in 1967, and "Plant Viruses," the fifth edition of which was published in 1974. He wrote for the general reader as well. "Viruses," published by Cambridge University Press in 1962, is an example.

Kenneth had many hobbies, particularly gardening and butterfly collecting. In his youth he was a runner and tennis player and in his later years an avid cyclist. After Kenneth returned to Cambridge following his postretirement stays in Pittsburgh and Austin, he developed serious problems in both hips. Sadly, he reported in correspondence with other editors that he had to trade his bicycle in for a wheelchair. However, hip joint replacements were totally successful, and in a footnote in one of his letters he reported joyfully that he had bought a new bicycle. He was then in his eighties.

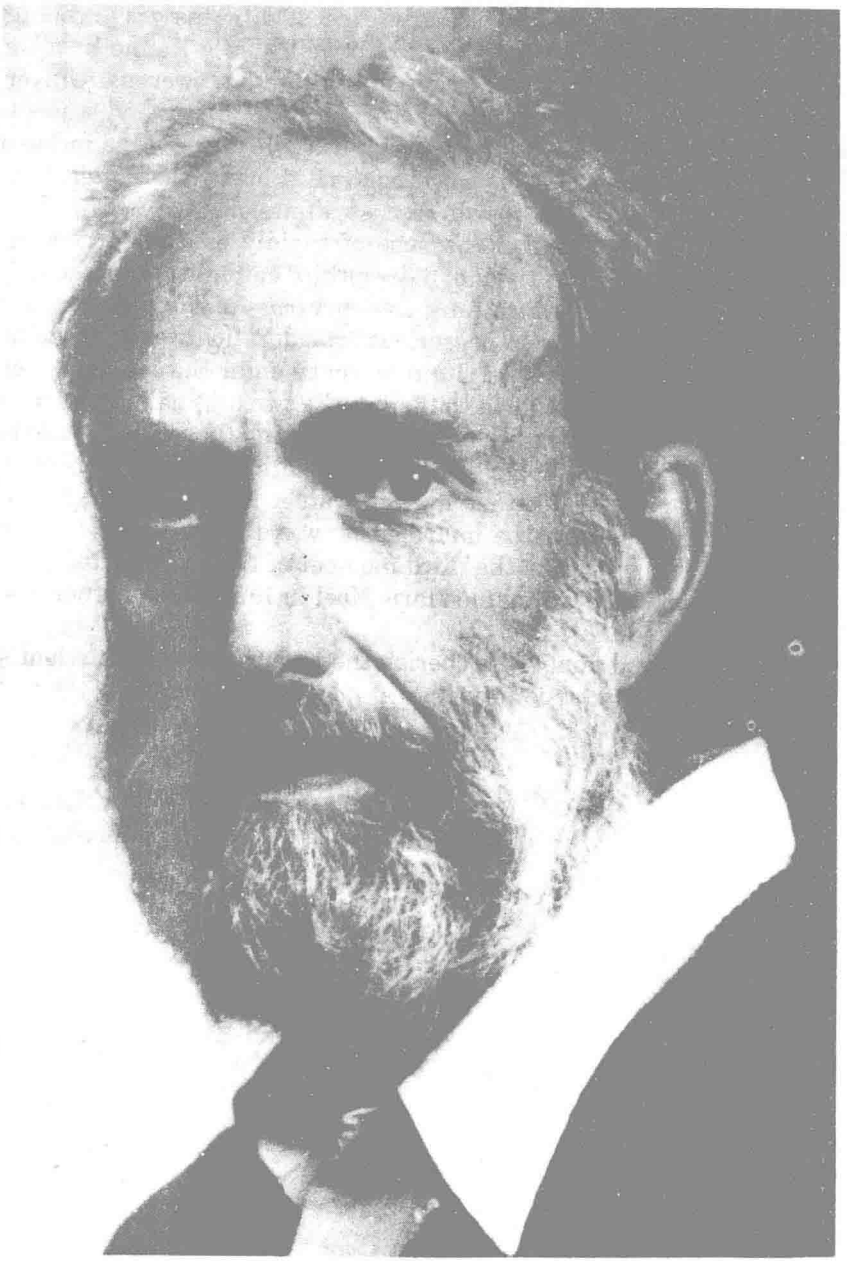
Kenneth was a charming, warmhearted, generous human being

with a wry sense of humor carefully concealed by his grave countenance from all but those who knew him well. While Kenneth was in Texas, a demented individual locked himself in the tower of a University building and shot with lethal accuracy at professors and students walking across campus. Kenneth was much alarmed by this incident because he walked that same path regularly. Shortly thereafter, Kenneth and the other editor met to discuss affairs of *Advances in Virus Research*. They agreed that, because of rapidly escalating developments in the field, it was time to invite a third editor active in the field of medical virology. Because *Advances in Virus Research* has always been international in its scope, serious consideration was given to inviting someone from Great Britain or continental Europe. However, the view was finally put forth that since the two original editors were in Austin and Pittsburgh, communication among the editors would be facilitated if one were chosen from North America. Kenneth concurred in the decision and agreed that an American be invited, but dryly added the condition that he be unarmed. It was thus that the late Dr. Frederik B. Bang became the third member of the editorial team.

Dr. Smith married Germaine Marie Noël in 1923. She and their son, Marcel, survive him.

The Editors and publishers cherish the memory of a great scientist and a delightful and true friend.

MAX A. LAUFFER
KARL MARAMOROSCH



FREDERIK B. BANG (1916–1981)

FREDERIK B. BANG

Dr. Frederik Barry Bang, an editor of *Advances in Virus Research* since 1969, died suddenly on October 3, 1981 at John F. Kennedy Airport en route to Europe. He was scheduled to present important papers in the Federal Republic of Germany and in Sweden on the contributions to human health of research in invertebrate pathology and marine biology.

Frederik Bang, the son of A. F. and Carol Klee Bang and the grandson of the Danish investigator who pioneered research on bovine brucellosis, a malady known to this day as Bang's disease, was born on November 5, 1916, in Philadelphia. He was educated at The Johns Hopkins University: A.B. (1935) and M.D. (1939). Following graduation from medical school, he interned for one year at the U. S. Marine Hospital in Baltimore. He then spent a year in the laboratory of Ernest Goodpasture at Vanderbilt University as a National Research Council Fellow in Medicine. From 1941 to 1946 he was assistant in the Department of Animal Pathology at the Rockefeller Institute for Medical Research, Princeton, New Jersey. His work at Princeton was interrupted from 1943 to 1946 by service in the southwest Pacific and in the Philippines as an officer in the U. S. Army Medical Corps, where he advanced to the rank of major. He returned to The Johns Hopkins University Medical School in 1946 as assistant professor of medicine and was promoted to associate professor in 1949. In 1953 he transferred to the School of Hygiene and Public Health at Hopkins as professor and chairman of the Department of Parasitology. There, from 1955 until his death, he was professor and chairman of the Department of Pathobiology. He served as director of The Johns Hopkins Center for Medical Research in Calcutta, India from 1961 to 1973, and, after the Center was transferred to Dacca, Bangladesh, he continued as director until 1976. Dr. Bang was an enthusiastic devotee of the Marine Biological Laboratory in Woods Hole, Massachusetts, where he served since 1978 as instructor in charge of the annual course on the comparative pathology of marine invertebrates. He and his family maintained a home in Woods Hole, where he was plannning to retire to continue research at the Marine Biological Laboratory.

Dr. Bang was honored as a Fulbright Scholar from 1955 to 1956, when he worked at the National Institute for Medical Research, London, in the laboratory of Christopher Andrewes. In the summers of 1961 and 1964 he was a Guggenheim Fellow in the Station Biologique in Roscoff, France.

Frederik was a relentless investigator, both in the laboratory and in the field. He published exhaustively—more than 250 articles and reviews. His scientific interests were extremely broad. They ranged from the feeding habits of mosquitoes to population biology, from chemotherapy to vitamin deficiency diseases, from cell culture to electron microscopy, from protozoan parasites to viruses, from famine to viral oncology, and from man to marine invertebrates. Dr. Bang published contributions on the malarial parasite, the gonococcus, the swine influenza bacterium, and *Schistosomiasis japonica*. His viral research involved lymphopathia venerea virus, eastern, western, and St. Louis encephalitis viruses, pseudorabies virus, many strains of influenza virus, poliomyelitis virus, New Castle disease virus, hepatitis virus, Rous sarcoma virus, the mammary tumor inciter, and a laryngotracheitis virus. His collaborators from many parts of the world included dozens of able and distinguished investigators, among whom was his wife. Despite the breadth of his concerns, his primary interest was the pathogenesis of virus diseases.

Dr. Bang was a member of the American Association for the Advancement of Science, the American Society of Tropical Medicine and Hygiene, the American Institute of Biological Sciences, the Interurban Clinical Club, the American Association of Immunologists, the American Society of Clinical Investigation, and the American Society of Experimental Pathology. He was also a member of the Society of Experimental Biology and Medicine, the Marine Biology Association of India, the International Epidemiological Association, the American Society for Microbiology, the American Association of Pathologists, the American Society of Parasitologists, the Society of Invertebrate Pathology, Phi Beta Kappa, and Sigma Xi. His editorial services included, in addition to *Ad ances in Virus Research, Cahiers de Biologie Marine.*

Dr. Bang married Betsy Garrett in 1940. Mrs. Bang, two daughters, Caroline and Molly, and one son, Axel Frederik, survive him.

Fred was a well-informed, demandingly logical, intellectually honest, fair-minded man. The Editors will always remember him as a delightful friend and a valued colleague.

MAX A. LAUFFER
KARL MARAMOROSCH

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Anne M. Field

Virus Reference Laboratory
Central Public Health Laboratory
London, England

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I. Introduction

Diagnosis of viral infections by observation of virus particles in thin sections of infected tissues has been a continuing but perhaps rather underused technique for the last 30 years. Observation of virus particles in suspension in metal-shadowed preparations had some diagnostic applications, but when the negative staining technique was introduced in 1959 and, as a result, virus particles were more readily recognizable, diagnostic use of the electron microscope became extremely practical. The presence in the world of smallpox infection and the consequent necessity for rapid differentiation between the smallpox virus and other viruses established the electron microscope as an essential tool in a few selected laboratories. Naturally these instruments were utilized for other virus diagnostic problems and gradually experience accumulated. Confirmation of electron microscopy as a good diagnostic technique for samples direct from patients came in the late 1960s with hepatitis B serum testing. In the 1970s the essentially noncultivable fecal viruses of hepatitis A and various diarrheal conditions were discovered and in these studies electron microscopy played an indispensable role.

The purpose of this article is to review the development of the use of electron microscopy in viral diagnosis in the last 20 years and to place it in context with other laboratory techniques. The field covered is confined to medical viral diagnosis, but parallel developments have taken place in both veterinary and botanical fields and techniques derived from both these sources are included where relevant. Viral diagnostic electron microscopy in the medical field has been reviewed by Doane (1974), by Doane and Anderson (1977), by Donelli *et al.* (1979), and by Hsiung *et al.* (1979).

II. Viral Morphology

Virus particles have characteristic morphologies (i.e., shape, substructure, and size) which, because they are fundamental properties, are important in viral classification. Viral structure is thus the basis for the use of the electron microscope for diagnosis and viruses having the same structure constitute a morphologic group, which may be a family of viruses or a genus. Within a group individual viruses cannot be differentiated on appearance and more sophisticated methods of antigenic analysis must be used, but it is often sufficient for diagnostic purposes merely to place a virus within such a group. Many diagnoses

are made by recognition of the characteristic viral structure in the image displayed on the microscope screen and need not await confirmatory micrographs; for this an appreciation of the full range of viral morphology by the operator is essential.

The salient features of viral morphology as observed by negative staining and thin sectioning methods (Section III) are here briefly reviewed and illustrated diagrammatically in Fig. 1, and selected exam-

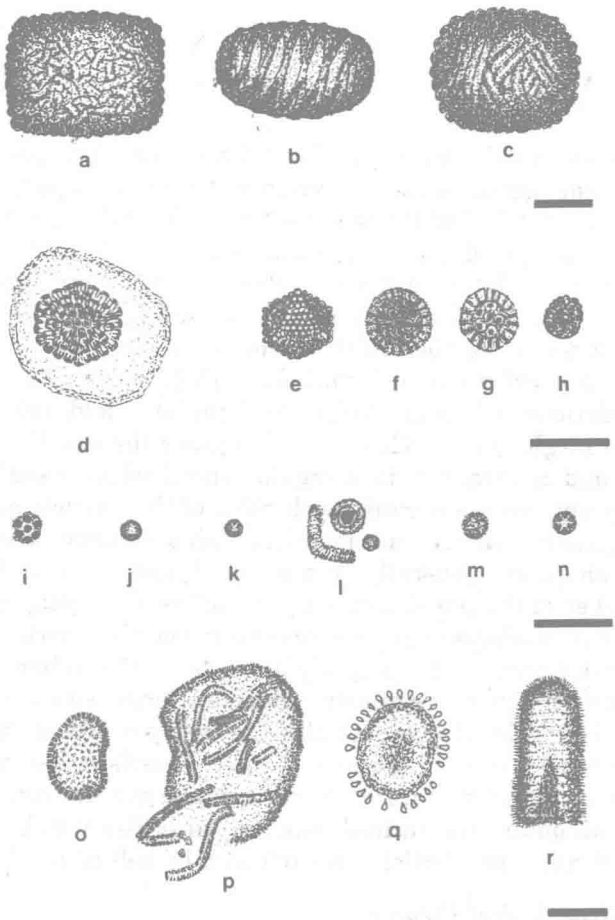

FIG. 1. Systematic morphology: the negatively stained morphology of virus particles represented diagrammatically. a, Orthopoxvirus; b, parapoxvirus; c, molluscum contagiosum virus; d, herpesvirus; e, adenovirus; f, reovirus; g, rotavirus; h, papovavirus; i, calicivirus; j, picornavirus; k, parvovirus; l, hepatitis B antigen; m, Norwalk agent; n, astrovirus; o, orthomyxovirus; p, paramyxovirus; q, coronavirus; r, rhabdovirus. Bars = 100 nm.

ples are illustrated photographically (Figs. 2 to 12). Reviews of viral structure have recently been published (Rabin and Jenson, 1967; Madeley, 1972; Dalton and Haguenau, 1973; Cheville, 1975). This review is not intended to be comprehensive but stresses the features with diagnostic significance and is largely based on personal observations and the reviews quoted above. Terminology is according to recent viral classification (REPORT, 1979).

A. Systematic Morphology

1. Poxviruses

Poxviruses are the largest and most complex virus particles. The *Orthopoxvirus* genus includes vaccinia, variola, cowpox, and monkeypox viruses, all of which can infect man. Negatively stained particles are brick-shaped, 220 to 270 nm long, and 180 to 220 nm wide. When penetrated by stain the particles appear larger than when unpenetrated. The latter display a random arrangement of 9-nm-wide surface filaments. Members of the *Parapoxvirus* genus causing human infections are orf virus and milker's nodule virus. The negatively stained particles are ovoid, 220 to 300 nm long, and 150 to 180 nm wide. The single surface filament is narrower than on *Orthopoxvirus* particles and is arranged in a regular spiral which usually gives a criss-cross appearance because both sides of the particle are imaged. Stain-penetrated particles are identical with orthopoxviruses except in the ovoid shape and generally greater length and lesser width. A probable member of the poxvirus family is molluscum contagiosum virus which has brick-shaped particles resembling orthopoxviruses but with more rounded corners. The slightly narrower surface filaments are arranged rather more regularly than on orthopoxviruses. Stain-penetrated particles closely resemble the orthopoxviruses except in the rounded corners. In thin sections of infected cells it has been shown that all poxviruses mature within a cytoplasmic matrix. In mature particles an outer coat encloses two lateral bodies which lie on each side of a dense core. Particles are released by cell lysis.

2. Large Icosahedral Viruses

Because of their large size and complex structure the poxviruses cannot be confused with other viruses. Some of the larger icosahedral viruses, although of different families, can resemble each other under some circumstances, particularly if damaged. The families concerned are the Herpesviridae, Adenoviridae, Reoviridae (including reoviruses,

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